An observational study using the radioligand [11C]-UCB-J for imaging synaptic density in healthy participants, patients with a psychotic disorder and their healthy siblings

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This study aims to investigate if and how synaptic density may underlie cognitive deficits and whether functional connectivity is the intermediate step. In patients with psychotic disorders, cognitive function and brain connectivity may be decreased...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Schizophrenia and other psychotic disorders
Study type	Observational non invasive

Summary

ID

NL-OMON49941

Source
ToetsingOnline

Brief title
Synaptic density in psychotic disorders

Condition

- Schizophrenia and other psychotic disorders

Synonym
cognition (thinking), Schizophrenia

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Cognitive functioning, Functional connectivity, Psychotic disorders, Synaptic density

Outcome measures

Primary outcome

MRI parameters:

• Functional connectivity defined in terms of GRAPH theory, i.e., number of

nodes and edges, minimal pathlengths and effectivity of the network

• Grey matter volumes as measured by MRI. MRI scans will be acquired on a

standard 3 Tesla Siemens clinical scanner located at the Radiology Department

of the University Medical Center Groningen.

• Metabolites concentrations as assessed with MRS.

PET parameters:

PET parameters are defined in a PET analysis plan and include:

• Specific/non-specific [11C]-UCB-J binding (expressed by volumes of

distribution)

• Time-activity courses

• The volume of distribution per region per subject

• Distribution volume ratios

Cognitive and clinical parameters:

• PANSS: Positive and Negative Syndrome Scale

• BACS: Brief assessment of cognition in schizophrenia

• Symbol Search: a measure of information processing speed derived from the

WAIS-IV

• Stroop task

• CASH-interview: Comprehensive Assessment of Symptoms and History

- the PRAAT language assesment interview

Secondary outcome

Not applicable

Study description

Background summary

Schizophrenia and related psychotic disorders (schizo-affective disorder and schizophreniform disorder) are severe mental disorders, placing a significant burden on global health. Patients suffer from a variety of psychotic, negative and cognitive symptoms. Additionally, they are at increased risk of developing metabolic syndrome and mortality with cardiovascular diseases is increased. The genetic liability for psychotic disorders includes important loci in the human leukocyte antigen (HLA) area, which predisposes subjects for increased and prolonged activation of microglia. Activated microglial cells have been reported to increase synaptic pruning in psychotic disorders, leaving the brain in suboptimal condition. The decreased synaptic density, resulting from accelerated pruning, is hypothesized to underlie cognitive dysfunction seen in the majority of patients with psychotic disorders. Potential ways how the loss of synaptic density may impair cognition is by affecting neuronal circuitry, which can be reflected in reduced functional connectivity as assessed with functional magnetic resonance imaging (fMRI). Although this theory has face-value, evidence to support it is currently absent, as studies invariably have either post-mortem material, which may evidence decreased synaptic density, or performance data on cognition and functional connectivity, but never the three together. Yet it is an important step to investigate whether and how decreased synaptic density in patients with psychotic disorders is the substrate of cognitive dysfunction and whether decreased functional connectivity is an intermediate step. It is now possible to measure these three

variables: synaptic density, cognitive functioning and functional connectivity at the same time since a new tracer has been developed to reflect synaptic density.
[11C]-UCB-J((R)-1-((3-(11C-methyl-11C)pyridin-4-yl)methyl)-4-(3,4,5-trifluorophenyl)pyrrolidin-2-one) exhibits excellent Positron Emission Tomography (PET) tracer characteristics, including short-term test re-test repeatability and reproducibility across brain regions.

Study objective

This study aims to investigate if and how synaptic density may underlie cognitive deficits and whether functional connectivity is the intermediate step. In patients with psychotic disorders, cognitive function and brain connectivity may be decreased as a consequence of their genetic vulnerability. However, the use of anti-psychotic medication and lack of education, secondary to early disease onset may reinforce this effect. In an attempt to disentangle genetic vulnerability from secondary disease and medication effects, we also invite first-degree family members of the patients to participate.

Study design

Mono-center, observational, cross-sectional, non-therapeutic study in healthy participants, schizophrenia-spectrum patients and their siblings.

Study burden and risks

All subjects will undergo one synaptic vesicle glycoprotein 2A (SV2a) PET scan. Subjects will receive approximately 370 MBq (10 mCi) of [11C]-UCB-J per PET study. A minimum of 270MBq (7.3 mCi) of activity is required in order to begin a scan. Participation in the study will entail a PET scan session of approximately 60 minutes. According to ICRP36, the radiation level of 1,7 mSv is within the category IIb, minor to moderate risk (1-10 mSv). The burden in radiation is comparable to the dose that passengers aboard an airplane receive during 25 or more transatlantic flights.
For anatomical reference, which is lacking in PET, an MRI scan of the subjects is needed, which is combined with the functional MRI scan. For all subjects, an MRI scan will be made in addition to the PET scan. The MRI scan will last 45 minutes and will pose no risk. Some people may become claustrophobic in the narrow MRI scanner, in which case the scan is aborted immediately, and subjects are freed instantly. The study has no direct benefit for the participants. In the case of patients and family, participation may increase their understanding of psychotic disorders. The risks associated with participation and the benefits to the individuals are low. The potential benefit to science and society in the future is considerable if the findings lead to more insight into the brain basis underlying cognitive deficits in psychotic disorders, as a treatment to decrease pruning may be a next step to

restore cognition.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. The participant understands the study and provides written informed consent
2. Must be between the age of 26-65
3. For patients: must have a diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder
4. For siblings: must have 1 brother or sister with a disorder specified under point 3. The sibling is not necessarily related to one of the participants from the patient group.
5. For controls: subjects must be free of any psychiatric or neurological disease and should not have any first- or second-degree relatives with one of

the disorders specified under point 3.
6. Dutch as native language

Exclusion criteria

1. Participation in a scientific research study during the past year involving radiation (or any other form of exposure to the same amount of radiation within the past year via, e.g., 25 or more transatlantic flights during the past year)
2. MRI incompatible implants in the body
3. The possibility of having metal particles in the eyes
4. Tattoo*s containing red pigments that form a safety risk
5. Dangerous or harmful behaviour (i.e. behaviour with a risk of severe physical injury, or actual physical injury inflicted, to self or others) occurred in the last 3 months
6. Pregnancy
7. Treatment with levetiracetam or brivaracetam (contraindication for [11C]-UCB-J)
8. Speech disorders (e.g., stuttering)
9. Uncorrected hearing disorder

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	08-07-2020
Enrollment:	78
Type:	Actual

Ethics review

Approved WMO Date:	19-12-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-02-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-04-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-10-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-12-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 27759
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL71100.042.19
Other	NL8046
OMON	NL-OMON27759